JOC*Note*

N-Isopropylidene-*N*′-2-nitrobenzenesulfonyl Hydrazine, a Reagent for Reduction of Alcohols via the Corresponding Monoalkyl Diazenes

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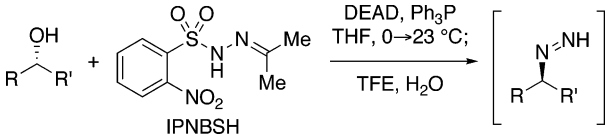
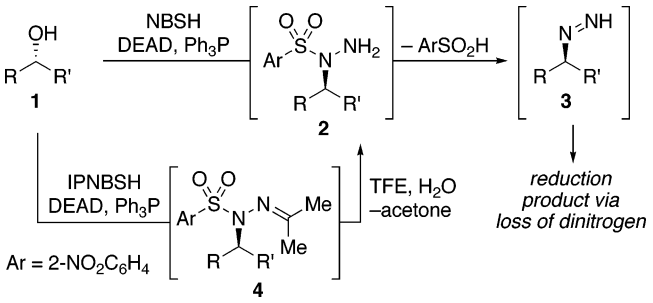


The reagent *N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine (IPNBSH) is used in the reduction of alcohols via the loss of dinitrogen from transiently formed monoalkyl diazene intermediates accessed by sequential Mitsunobu displacement, hydrolysis, and fragmentation under mild reaction conditions.

The loss of dinitrogen from monoalkyl diazene intermediates is common in a wide range of transformations in organic chemistry.[1,2] Several powerful methodologies for carbonyl reduction involve initial condensation with an arenesulfonyl hydrazine followed by reduction of the corresponding hydrazone leading to the loss of dinitrogen. In 1996, Myers reported a highly efficient, mild, and stereospecific conversion of a variety of propargylic alcohols to the corresponding allenes[3a] via a Mitsunobu[4] reaction using the reagent 2-nitrobenzenesulfonyl hydrazide[5] (NBSH). Subsequent reports discussed the use of NBSH in the reduction of allylic, benzylic, and saturated alcohols.[3b,c] This direct reduction of alcohols via the corresponding monoalkyl diazene intermediates under mild reaction conditions presents a highly versatile methodology for organic synthesis.[6] We recently reported the use of the related reagent *N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine (IPNBSH) for a difficult allylic reductive transposition step in our total syntheses of (−)-acylfulvene and (−)-irofulven.[7] Herein we report our results on the general utility of IPNBSH, a reagent complimentary to NBSH, for conversion of alcohols to the corresponding monoalkyl diazene intermediates.

SCHEME 1



The stereospecific displacement of an alcohol by the reagent NBSH under the Mitsunobu reaction conditions affords the corresponding 1,1-disubstituted sulfonyl hydrazine **2** (Scheme 1).[3] Warming of the reaction mixture to ambient temperature provides the corresponding monoalkyl diazene **3** by elimination of 2-nitrobenzenesulfinic acid. Sigmatropic[3a,b] loss of dinitrogen from the unsaturated monoalkyl diazene or expulsion of dinitrogen via a free-radical[3c] pathway from the saturated monoalkyl diazene affords the corresponding reduction product. The thermal sensitivity of NBSH in solution and the corresponding Mitsunobu adduct **2** necessitate the execution of the initial step in these transformations at subambient temperatures (−30 to −15 °C). Lower reaction temperatures obviate a competitive and undesired Mitsunobu reaction of the alcohol substrate with 2-nitrobenzenesulfinic acid, the thermal decomposition[8] product of NBSH or adduct **2**.[3] For less reactive alcohols, the use of higher substrate concentrations and excess reagents in *N*-methyl morpholine has been described.[3b,c]

We recently found the use of the reagent IPNBSH to be advantageous over NBSH in a surprisingly difficult[9] reductive

(1) For representative examples, see: (a) Szmant, H. H.; Harnsberger, H. F.; Butler, T. J.; Barie, W. P. *J. Org. Chem.* **1952**, *74*, 2724. (b) Nickon, A.; Hill, A. S. *J. Am. Chem. Soc.* **1964**, *86*, 1152. (c) Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7016. (d) Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923. (e) Kabalka, G. W.; Chandler, J. H. *Synth. Commun.* **1979**, *9*, 275. (f) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717. (g) Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208. (h) Myers, A. G.; Finney, N. S. *J. Am. Chem. Soc.* **1990**, *112*, 9641. (i) Guziec, F. S., Jr.; Wei, D. *J. Org. Chem.* **1992**, *57*, 3772. (j) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. (k) Bregant, T. M.; Groppe, J.; Little, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 3635. (l) Ott, G. R.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1475. (m) Chai, Y.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2003**, *5*, 1039. (n) Sammis, G. M.; Flamme, E. M.; Xie, H.; Ho, D. M.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8612.

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(3) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (b) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841. (c) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572.

(4) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1982**, *42*, 335.

(5) (a) Dann, A. T.; Davies, W. *J. Chem. Soc.* **1929**, 1050. (b) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507. (c) Myers, A. G.; Movassaghi M. In *e-Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed; John Wiley & Sons: New York, 2003.

(6) For examples in the utility of NBSH in synthesis, see: (a) Shepard, M. S.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597. (b) Corey, E. J.; Huang, A. X. *J. Am. Chem. Soc.* **1999**, *121*, 710. (c) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633. (d) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562. (e) Charette, A. B.; Jolicoeur, E.; Bydlinski, G. A. S. *Org. Lett.* **2001**, *3*, 3293. (f) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771. (g) Regás, D.; Afonso, M. M.; Rodríguez, M. L.; Palenzuela, J. A. *J. Org. Chem.* **2003**, *68*, 7845. (h) McGrath, M. J.; Fletcher, M. T.; König, W. A.; Moore, C. J.; Cribb, B. W.; Allsopp, P. G.; Kitching, W. *J. Org. Chem.* **2003**, *68*, 3739. (i) Ng, S.-S., Jamison, T. F. *Tetrahedron* **2005**, *61*, 11405. (j) Michael, F. E.; Duncan, A. P.; Sweeney, Z. K.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 1752. (k) Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. *Science* **2005**, *308*, 395.

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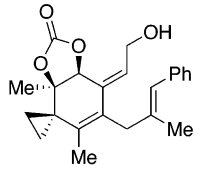
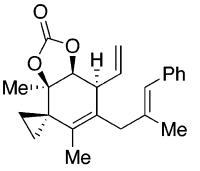
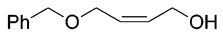
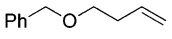
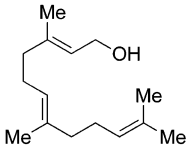
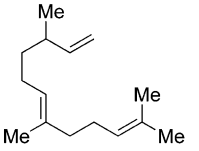
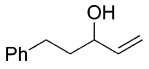
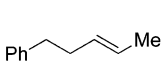
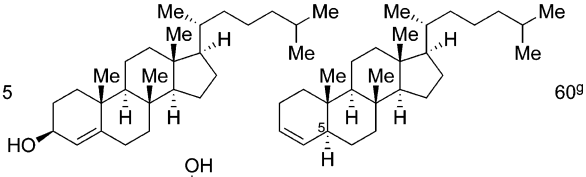
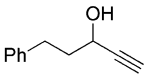
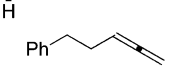
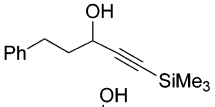
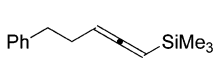
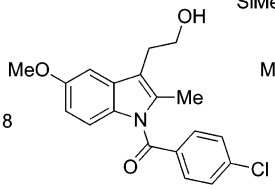
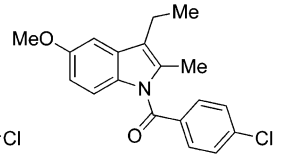
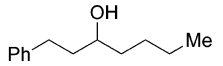
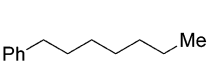
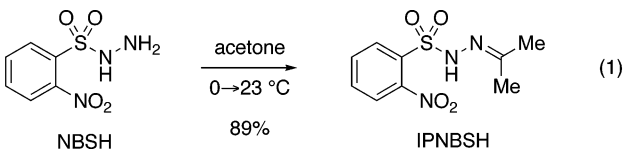
TABLE 1. Reduction of Alcohols Using IPNBSH[a]

Entry	Substrate	Product	Yield(%)[b]
1			71[c]
2			84[d]
3			82[d,e]
4			69[f]
5			60[g]
6			70
7			87
8			87[h]
9			35[h]

[a] Conditions: Ph_3P (1.2 equiv), DEAD (1.2 equiv), IPNBSH (1.2 equiv), THF (0.1 M), 0 → 23 °C, 2 h; TFE−H_2O (1:1), 2 h. [b] Average of two experiments. [c] Reference 7. [d] Hydrolysis step required 3 h. [e] Mitsunobu reaction was complete in 15 min. [f] *E*:*Z* = 93:7. [g] 2.0 equiv of reagents was used; contains <8% of C5-diastereomer. [h] 1.6 and 2.5 equiv of reagents was used in entries 8 and 9, respectively; $PhNHNH_2$ (5.0 equiv) was used in place of TFE−H_2O.

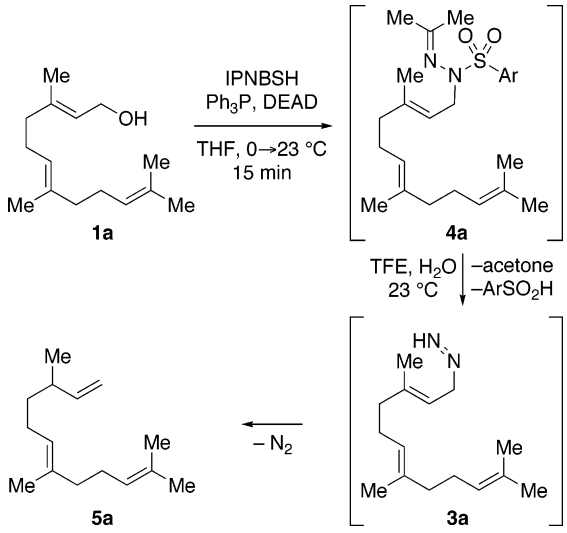
allylic transposition reaction.[7] In reduction of the substrate in entry 1 of Table 1, IPNBSH provided greater flexibility with respect to solvent choice, reaction temperature, order of addition, and concentration of substrate and reagents. As shown in Scheme 1, the Mitsunobu displacement of an alcohol with IPNBSH results in the stable and isolable arenesulfonyl hydrazone **4**. We developed mild reaction conditions for in situ hydrolysis of hydrazone **4** to the same hydrazine **2** accessed using NBSH (Scheme 1).



(1)

IPNBSH can be prepared by dissolution of the readily available NBSH[5] in acetone (eq 1). For optimal results, IPNBSH is triturated with hexanes to give the desired reagent as a white solid. Comparison of the X-ray structure of IPNBSH[10] with that of the closely related acetone *p*-toluenesulfonyl hydrazone[11] reveals longer C−S (1.774 vs 1.753 Å) and slightly shorter N(2)−S (1.636 vs 1.637 Å) bonds consistent with greater interaction between the nitrogen(2) and sulfur in IPNBSH. The smaller N−N−S bond angle found in IPNBSH (112.4° vs 114.1°) was expected to reduce the steric interaction of the *syn*-coplanar N-H and C-Me groups.

SCHEME 2



Significantly, the greater thermal stability of IPNBSH compared to that of NBSH was expected to provide flexibility for the Mitsunobu reaction while offering equally rapid thermal fragmentation after hydrolysis of the adduct **4** (Scheme 1). For comparison, heating a solution of IPNBSH in DMSO-d_6 (0.02 M) at 50 °C for 30 min did not result in decomposition, whereas a significant quantity of NBSH (~60%) was found to fragment under the same conditions. Solutions of IPNBSH as described above did not decompose at 75 or 100 °C after 30 min, whereas considerable decomposition was observed at 150 °C within minutes. The greater thermal stability of IPNBSH allows it to be stored at room temperature for several months.[5b,c,12]

The utility of IPNBSH in the challenging[7] reductive allylic transposition mentioned above prompted our evaluation of this reagent's broader utility for organic synthesis. Addition of diethylazodicarboxylate (DEAD, 1.20 equiv) to a solution of *trans*,*trans*-farnesol (**1a**, 1 equiv, Scheme 2), IPNBSH (1.21 equiv), and triphenylphosphine (Ph_3P, 1.21 equiv) in THF (9.0 mL) rapidly (15 min) provided the desired Mitsunobu adduct **4a** in 86% isolated yield. The isolation of **4a** is not necessary, and its direct hydrolysis under optimal conditions was achieved by introduction of trifluoroethanol−water (1:1) upon completion of the Mitsunobu reaction.[13] The hydrolysis step results in

(9) For other examples, see: (a) Ott, G. R.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1475. (b) The use of high reaction temperatures described in Vostrikov, N. S.; Vasikov, V. Z.; Miftakhov, M. S. *Russ. J. Org. Chem.* **2005**, *41*, 967 likely cause decomposition of NBSH.

(10) See Supporting Information for the crystal structure of IPNBSH.

(11) Ojala, C. R.; Ojala, W. H.; Pennamon, S. Y.; Gleason, W. B. *Acta Crystallogr.* **1998**, *C54*, 57.

(12) Due to potential toxicity and flammability of IPNBSH similar to that of related arenesulfonylhydrazides (e.g., *p*-toluenesulfonylhydrazide), prudent experimental practices should be followed in handling of IPNBSH with gloves under inert atmosphere. See *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed; John Wiley & Sons: New York, 1995; Vol. 7, p 4953.

fragmentation of 2-nitrobenzenesulfinic acid followed by sigmatropic loss of dinitrogen to give the triene **5a** in 87% isolated yield. The ease of hydrolysis of these hydrazones under mild conditions is likely due to the rapid fragmentation of the corresponding sulfonyl hydrazine derivatives at room temperature.[14]

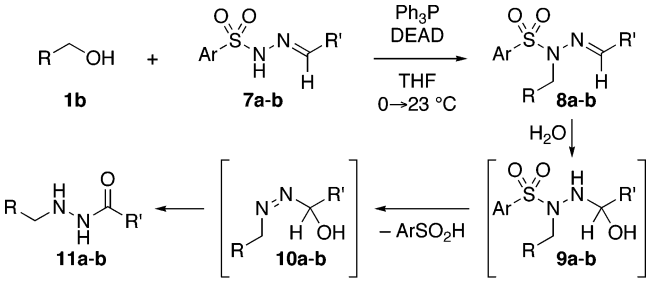
A uniform set of reaction conditions proved effective for a single-step reduction of a range of alcohols (Table 1). Allylic alcohols (Table 1, entries 1−5) and propargylic alcohols (Table 1, entries 6 and 7) provided the desired reduction products via the expected sigmatropic loss of dinitrogen from the intermediate monoalkyl diazenes generated by in situ hydrolysis. For unhindered primary alcohols the reaction could be conducted at even lower concentration (0.05 M) and subambient temperatures with equal efficiency. The use of IPNBSH allowed the use of other solvents (e.g., toluene, fluorobenzene, and chlorobenzene) in place of THF with similar results.

Interestingly, while the Mitsunobu reaction with the primary alcohol in entry 8 of Table 1 proceeded smoothly under standard conditions (adduct isolated in 93% yield), the hydrolysis of the corresponding hydrazone adduct **4** under the conditions used for propargylic and allylic substrates proved ineffective, affording less than 20% yield of the desired reduction product.[15]

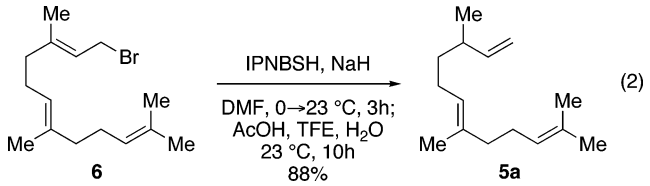
We reasoned that although slow hydrolysis and generation of unsaturated (propargylic and allylic) monoalkyl diazenes led to an efficient sigmatropic loss of dinitrogen, the loss of dinitrogen from saturated monoalkyl diazenes would be optimal at higher concentrations of the diazene intermediate.[16] The replacement of the hydrolysis step with a hydrazone exchange reaction (phenylhydrazine) reduced the time for the complete consumption of the Mitsunobu adduct from 4 h to 30 min (TLC analysis).[17] A limitation of IPNBSH is its greater sensitivity toward sterically hindered substrates as compared to NBSH. For example, the Mitsunobu reaction with the saturated secondary alcohol in entry 9 of Table 1 proved difficult as compared to the reaction of unsaturated secondary alcohols (Table 1, entries 4−7).[18] The use of more forcing reaction conditions with the alcohol in entry 9 of Table 1 did not increase the isolated yield of the desired product and returned the starting alcohol.[19]

The thermal stability of IPNBSH allows for unique transformations such as the one shown in eq 2. N-Alkylation of the corresponding sodium sulfonamide of IPNBSH with allylic bromide **6** followed by in situ hydrolysis afforded the desired terminal alkene **5a** via sigmatropic loss of dinitrogen. This single-step N-alkylation−reduction strategy offers a valuable alternative to the approach based on the Mitsunobu reaction.[9a]

SCHEME 3



Ar = 2-$NO_2C_6H_4$; R = (4-chloro-phenyl)-[5-methoxy-2-methyl-3-(2-ethyl)-indol-1-yl]-methanone; **7a-11a**, R' = Me; **7b-11b**, R' = ^{t}Bu



In addition to IPNBSH, we examined a series of other hydrazone derivatives as potential reagents for the conversion of alcohols to the corresponding monoalkyl diazenes. These included the 2-nitrobenzenesulfonyl hydrazones of trifluoroacetone, dichloroacetone, cyclobutanone, benzaldehyde, acetaldehyde, and trimethylacetaldehyde, in addition to methanesulfonyl hydrazones of acetone and benzaldehyde. IPNBSH was identified as the best reagent on the basis of optimal reactivity in the Mitsunobu reaction and ease of hydrolysis of the corresponding adduct. Interestingly, although the Mitsunobu reaction of the aldehyde hydrazone derivatives proceeded with efficiency equal to that of IPNBSH, their hydrolysis gave the corresponding carbonyl hydrazide and not the expected reduction product (Scheme 3). This is likely due to isomerization[20] of transient α-hydroxyalkyldiazene intermediates **10a**−**b**.

In conclusion, the reagent IPNBSH serves as a reagent complementary to NBSH for conversion of alcohols to the corresponding reduction products via monoalkyl diazene intermediates. Attractive features of this reagent include ease of preparation, storage, and use due to excellent thermal stability. IPNBSH offers flexibility with respect to choice of reaction solvent, reaction temperature, order of addition, and concentration of substrate and reagents in the Mitsunobu reaction. We expect IPNBSH will find applications in unique transformations such as that illustrated in eq 2.

Experimental Section

(*E*)-3,7,11-Trimethyldodeca-1,6,10-triene (5a, Table 1, entry 3). DEAD (74 μL, 0.47 mmol, 1.2 equiv) was added dropwise to a solution of IPNBSH (122 mg, 0.474 mmol, 1.21 equiv), *trans*,*trans*-farnesol (**1a**, 0.100 mL, 0.393 mmol, 1 equiv), and triphenylphosphine (124 mg, 0.473 mmol, 1.21 equiv) in anhydrous THF (9.0 mL) at 0 °C under an argon atmosphere. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 20 min, a mixture of trifluoroethanol and water (1:1, 4.5 mL) was added to the reaction mixture to enable formation of the allylic diazene

(13) These conditions for the hydrolysis step were found to be superior to others explored, including the use of substoichiometric quantities of acetic acid or $Sc(OTf)_3$ or the use of other co-solvents (MeOH and EtOH).

(14) Consistent with this hypothesis, hydrolysis of the Mitsunobu adducts of secondary alcohols is faster than with those derived from primary alcohols.

(15) Addition of acetic acid, 2,6-lutidine, or 1,4-cyclohexadiene and the use of ethanedithiol instead of water did not improve the yield of the reduction product.

(16) A faster release of the sulfonyl hydrazine derivative **2** and formation of the diazene intermediate **3** could provide a more efficient free-radical loss of dinitrogen. Please see ref 2 and Myers, A. G.; Movassaghi, M.; Zheng, B. *Tetrahedron Lett.* **1997**, *38*, 6569.

(17) The addition of phenylhydrazine was only necessary in the deoxygenation of saturated alcohols.

(18) For comparison, the use of NBSH in the reduction of the saturated secondary alcohol in entry 9 of Table 1 under optimum reaction conditions provided the desired deoxygenated product in 80% yield. See ref 3c.

(19) Unfortunately, various procedural changes described in a more recent and related report (Keith, J. M.; Gomez, L. *J. Org. Chem.* **2006**, *71*, 7113) did not provide any advantage over our original reaction conditions in ref 7 for the use of IPNBSH in the Mitsunobu reaction.

(20) Tezuka, T.; Otsuka, T.; Wang, P.-C.; Murata, M. *Tetrahedron Lett.* **1986**, *27*, 3627.

intermediate. After 3 h, the reaction mixture was partitioned between diethyl ether (25 mL) and water (25 mL), and the aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (100% ^{n}pentane) to give triene **5a** (71 mg, 87%). All spectroscopic data were in agreement with literature.[21] TLC (40% ethyl acetate in hexanes) R_f: 0.8 (CAM, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ 5.25−5.15 (m, 1H), 5.13−5.10 (m, 2H), 4.99 (t, 1H, J = 2.0 Hz), 4.94−4.91 (m, 2H), 2.14−1.98 (m, 7H), 1.69 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.36−1.33 (m, 2H), 0.99 (d, 3H, J = 8 Hz). ^{13}C NMR (500 MHz, $CDCl_3$, 20 °C): δ 145.0, 135.1, 131.5, 124.7, 124.6, 112.7, 39.9, 37.5, 36.9, 26.9, 25.9, 25.8, 20.4, 20.4, 17.9, 16.2. MS (*m*/*z*) $C_{15}H_{26}$ $[M]^+$: 206. FTIR (thin film): 3077 (m), 2966 (s), 2915 (s), 2856 (s), 1640 (m), 1453 (s), 1376 (s).

5-Phenylpenta-1,2-diene (Table 1, Entry 6). DEAD (67.5 μL, 0.429 mmol, 1.20 equiv) was added dropwise to a solution of IPNBSH (110 mg, 0.429 mmol, 1.20 equiv), 5-phenylpent-1-yn-3-ol (57 mg, 0.36 mmol, 1 equiv), and triphenylphosphine (112 mg, 0.428 mmol, 1.20 equiv) in anhydrous THF (3.5 mL) at 0 °C under an argon atmosphere. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 2 h, a mixture of trifluroethanol and water (1:1, 1.7 mL) was added to the reaction mixture to enable the formation of the propargylic diazene intermediate. After 2 h, the reaction mixture was partitioned between ^{n}pentane (25 mL) and water (25 mL). The organic layer was washed with water (2 × 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (100% ^{n}pentane) to give the allene (36 mg, 70%). All spectroscopic data were in agreement with the literature.[22] ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ 7.31−7.28 (m, 2H), 7.22−7.21 (m, 3H), 5.17 (tt, 1H, J = 13.2, 6.8 Hz), 4.69 (dt, 2H, J = 6.8, 3.2 Hz), 2.75 (t, 2H, J = 7.6 Hz), 2.35−2.32 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$, 20 °C): δ 208.8, 142.0, 128.7, 128.5, 126.1, 89.6, 75.3, 35.6, 30.2. MS (*m*/*z*) $C_{11}H_{12}$ $[M]^+$: 144. FTIR (thin film): 3027 (s), 2922 (s), 2855 (s), 1955 (s), 1495 (m), 1453 (m).

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Supporting Information Available: Experimental procedures, spectroscopic data for all new compounds, and the X-ray structure of IPNBSH in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Ohno, H.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* **2002**, *67*, 1359.